

NEWSLETTER4

ERA-NET on Cardiovascular Diseases (ERA-CVD), Joint Transnational Call 2018 (JTC2018)

“Transnational Cardiovascular Research Projects driven by Early Career Scientists”

In January 2018 ERA-CVD published its 3rd Joint Transnational Call (JTC 2018) for “Cardiovascular Research Projects driven by Early Career Scientists - ECS”. This was a novum as the JTC addressed exclusively a specific group of researchers, but was thematically open. JTC2018 aims at enabling ESCs in different countries to build an effective collaboration on common multidisciplinary research consortia. The call intends to promote cooperation and interchange between ECS in cardiovascular research and thus enabling international collaboration and new consortia establishment. Therefore JTC2018 will support the next generation of cardiovascular researchers by funding 14 projects with a budget of over 11 Mio €. The research consortia are based on complementarities and sharing of expertise with a translational focus as can be seen on the following pages. Altogether 50 research groups comprise 14 coordinators and 34 project partners and 2 associated groups with their own funding from 13 countries (diagram 1). The majority of researchers (77%) are affiliated with academic and 21% with clinical health institutions (diagram 2). Another success of this JTC is the participation of private for-profit and not-for-profit entities (12%) as indication for translational approaches (diagram 3). 37% of female researchers participate in all projects (diagram 4), and 29% are coordinators (diagram 5). These numbers are encouraging, but can still be improved.

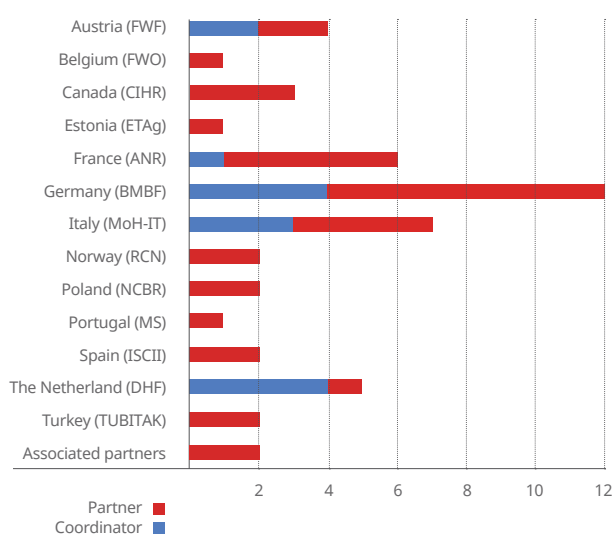


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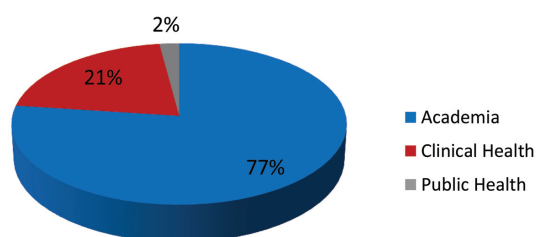
According to the new EU General Data Protection Regulation (GDPR) the ERA-CVD webpage informs on respective policies

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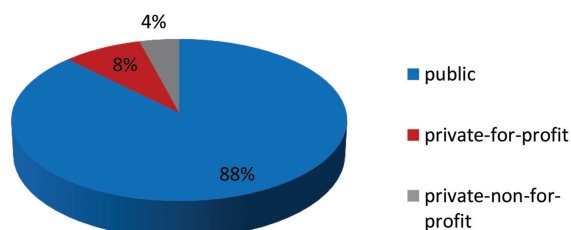
- ① 50 research groups comprise 14 coordinators and 36 project partners from 13 countries



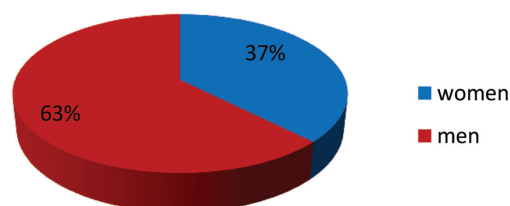
- ② The majority of researchers with 77% are affiliated with academic and 21% with clinical health institutions



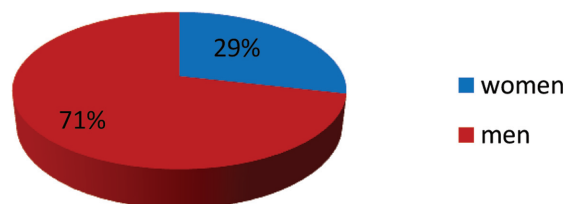
- ③ 12% participation of private for-profit and not-for-profit entities



- ④ Female researchers participate with 37% in all projects



- ⑤ Female researchers participate with 29% as coordinators



ERA-CVD NEWS

ERA-CVD will announce the Joint Transnational Call for Proposals 2019 at the beginning of 2019. JTC2019 will aim again at enabling Early Career Scientists in different countries to build an effective collaboration and interchange on common multidisciplinary research projects.

On August 27th, 2018 the EPCA ceremony took place at the European Society of Cardiology congress in Munich (<https://www.era-cvd.eu/376.php>). The awardee Dr. Shashi Kumar Gupta from the Institute of Molecular and Translational Therapeutic Strategies in Hannover Medical School, Germany was honored by ERA-CVD and gave an online interview.

The announcement of the call for Excellent Paper on Cardiovascular research Award 2019 will take place on January 2019.



Daniela Carnevale



NEMO-IMMUNE against HF

Neural MODulation of IMMUNE system to shape cardiac remodeling to chronic arterial hypertension and counteract Heart Failure

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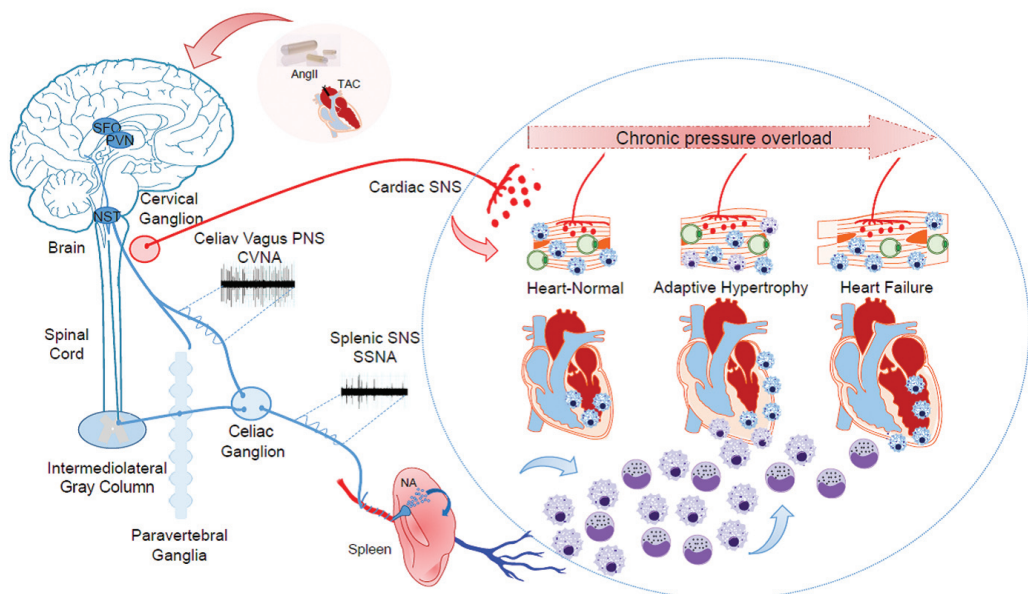
Partners:

Slava Epelman, Toronto General Hospital Research Institute, Canada

Sarah-Lena Puhl, Ludwig-Maximilians-University, Germany

Tomasz Pawel Mikolajczyk, Jagiellonian University Medical College, Poland

Hypertensive heart disease is one of the leading causes of disability and death associated with high blood pressure. When it becomes chronic, it leads to heart failure with a preserved ejection fraction and it could even worsen left ventricle function, leading to reduced ejection fraction. The cardiac remodeling as a result of hypertensive heart disease, may be caused by different components mutually interacting. We recently discovered that the autonomic nervous system (ANS), the main regulator of cardiac function, modulates immune functions involved in cardiovascular diseases. Since immune cells and burden of inflammation in pericardial adipose tissue (PAT) control myocardium's ability to withstand hypertension, our hypothesis is that neuroimmune interactions are required to shape left ventricle adaptive responses to hypertension. The network of this project will connect combined expertise to address how autonomic nervous system modulations, immune cells and pericardial adipose tissue, modulate cardiac scenario during hypertension, and how they influence the development of heart failure, trying to translate the results to human pathology.





Peter P. Rainer



AIR-MI

Adaptive Immune Responses in the wounded heart: novel diagnostic and therapeutic opportunities

Coordinator:

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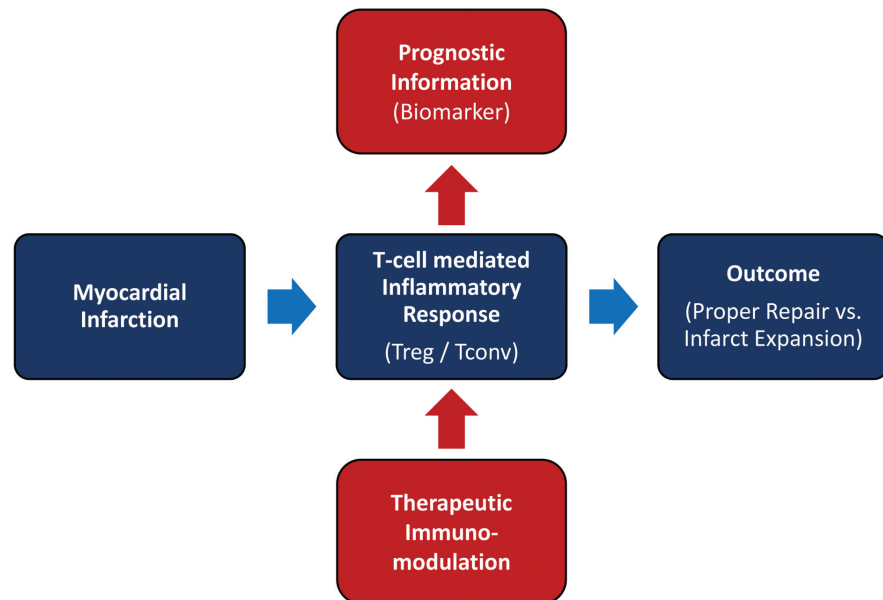
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Encarnita Mariotti-Ferrandiz, Sorbonne Université, France



Myocardial infarction and ensuing ischemic heart disease cause tremendous suffering and economic damage. Despite major advances in their treatment, molecular repair processes in the injured heart remain poorly understood. Consequently, we often cannot identify patients with inadequate repair before heart function deteriorates to a critical stage. Here, we propose that inflammatory processes, particularly T-cell mediated adaptive immune responses, critically regulate early cardiac repair. In our consortium, we will thus dissect T-cell responses in patients suffering from myocardial infarction using cutting-edge technologies such as next generation sequencing and correlate them with clinical outcomes. Further, we will integrate the results with data derived from mechanistic preclinical disease models investigating the role of adaptive immunity in myocardial infarction healing. These experiments will lay the fundament for developing novel immune-based prognostic tools and innovative treatment concepts in patients suffering from myocardial infarction and ischemic heart disease.



Christian Bär



INNOVATION

Investigating long non-coding RNA regulated pathways driving cardiac regeneration

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Partners:

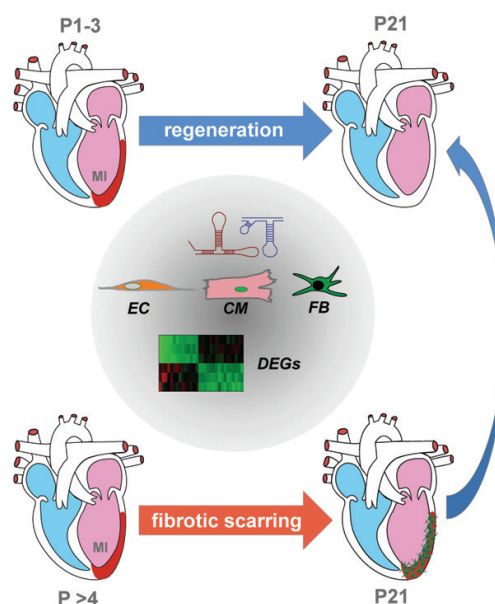
Reinier Boon, VU University Medical Center, The Netherlands

Bernhard Johannes Haubner, Innsbruck Medical University, Austria

Nuno Guimarães-Camboa, IRCCS Istituto Clinico Humanitas, Italy

Bruno Bernardes de Jesus, IBIMED, University of Aveiro, Portugal

One of the main causes underlying the high death toll of cardiovascular disease is the lack of significant cardiac regeneration of the adult heart. In marked contrast, for a short period of time after birth, newborn mice and possibly humans can fully regenerate the heart after a heart attack. INNOVATION aims to decipher the molecular circuitries underlying the striking difference between newborn heart regeneration and fibrotic infarct healing of the adult heart. INNOVATION particularly focuses on the “dark matter” of the genome which is, among other forms of RNA, comprised of tens of thousands long non-coding RNA (lncRNA). Although relatively unexplored, it has become evident that lncRNAs are required for the establishment and maintenance of normal gene expression networks, thus controlling developmental and disease processes. Our main goal is to identify lncRNA signatures in the newborn heart that can be exploited to devise novel regenerative strategies in the adult and in particular the diseased heart.



Aims:

- I. Sex and cell type specific lncRNA atlas of the regenerating heart
- II. Functional in vitro & in vivo investigation of lncRNAs in major cardiac cell types
- III. lncRNA-based therapeutic approaches to enhance cardiac regeneration



Joost Lumens



EMPATHY

Electromechanical presages of sudden cardiac death in the young: integrating imaging, modelling and genetics for patient stratification

Coordinator:

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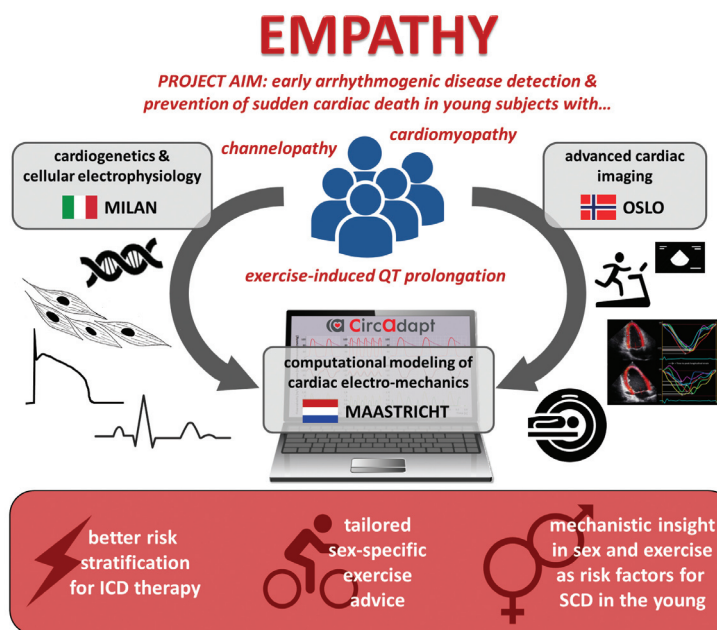
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In the young (<40 years), sudden cardiac death (SCD) is often the first manifestation of a genetic cardiac disease causing lethal arrhythmias. Both male gender and physical exercise are known risk factors for SCD in this vulnerable population. Current mechanistic

understanding of how gender-related and environmental factors, such as exercise, interact with a pro-arrhythmic substrate and trigger life-threatening arrhythmias is limited. This lack of knowledge makes the identification of those at risk for SCD extremely difficult. The EMPATHY project aims to unravel the complex pro-arrhythmic electro-mechanical interactions in the apparently healthy yet vulnerable hosts of genetic cardiac diseases by combining three different but highly complementary scientific fields, being clinical cardiac imaging (OSLO), genetics and cellular electrophysiology (MILAN), and multi-scale computational modelling (MAASTRICHT). We expect that the integrative EMPATHY approach will reveal novel genetic and electro-mechanical signatures of arrhythmogenic diseases, enabling earlier disease recognition, personalized therapeutic intervention, and effective prevention of SCD in the young.



Iwan W. Schie



MultiFib

Multimodal Fibre optic probe for highly resolved in vivo localization of cardiac Fibre

Coordinator:

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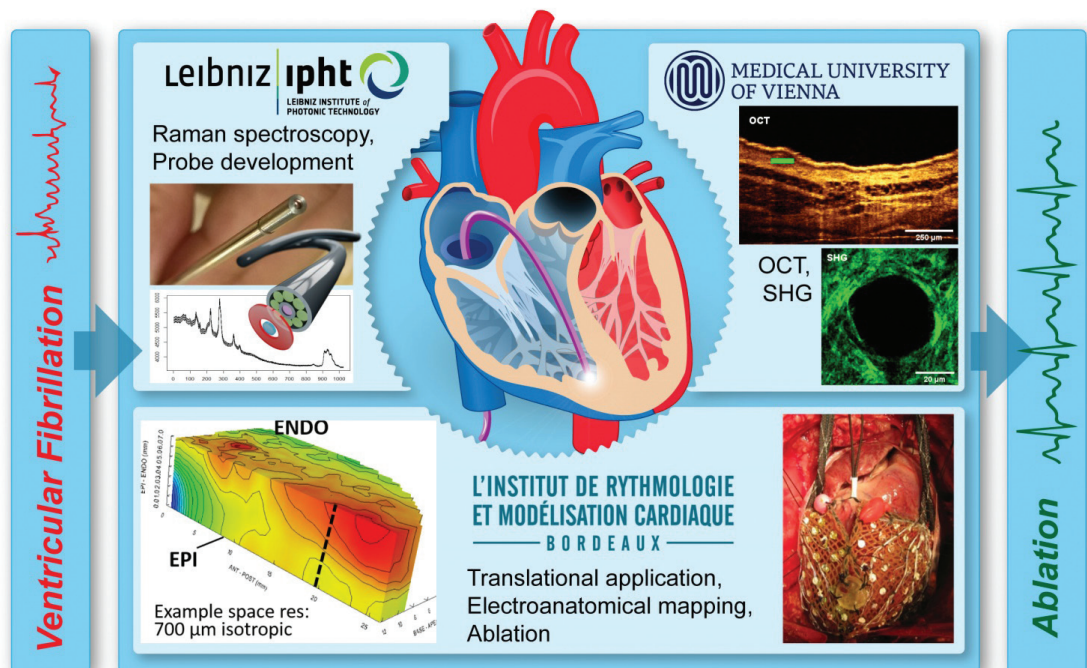
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Sudden cardiac death (SCD) accounts for 350,000 deaths each year in Europe alone. A major cause of SCD is a lethal cardiac rhythm disturbance, ventricular fibrillation (VF), resulting from structural heart disease. Sufferers are often only diagnosed at the event of SCD. Therefore, only a minority of patients are eligible for targeted curative treatments, such as ablation therapy. The project MultiFib aims to develop a multimodal imaging fibre probe capable of combined morphological and biochemical characterization of arrhythmogenic substrates at high optical resolutions as a guidance tool for cardiac ablation. The project will enable structural and biochemical mapping in conjunction with conventional electrical measures for an unprecedented assessment of myocardial properties and identification of pathological substrates. Furthermore, the project aims to provide a means to assess in real-time ablation efficacy.



Niels P. Riksen



MEMORY

Trained iMmunity in bonE MarrOw progenitors as dRiver of atherosclerosis in obesitY

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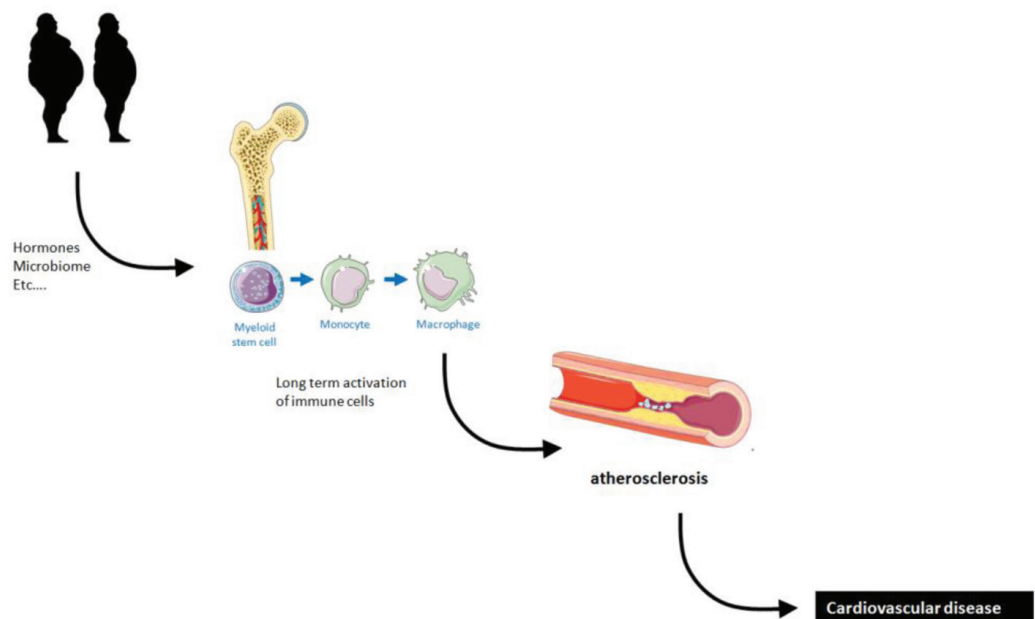
Hafid Ait-Oufella, St-Antoine Hospital and Inserm U97 Team "Immunity, inflammation and cardiovascular diseases" , France

Due to the worldwide adoption of Western lifestyle, the prevalence of obesity increases exponentially. Obesity is an important risk factor for atherosclerotic cardiovascular disease, including heart attacks and strokes. The ultimate aim of this proposal is to understand how Western type diet and obesity induce atherosclerosis.

We focus on the innate immune system, since this importantly contributes to atherosclerosis and we have recently shown that substances that can induce cardiovascular disease (such as cholesterol particles) can lead to a long-term activation of the innate immune system.

We propose that Western type diet and obesity changes the development of the innate immune system in the bone marrow in such a way that they are prone to stimulate the development of atherosclerosis.

Our results potentially can reveal novel mechanism that contribute to cardiovascular disease in subjects with obesity that can be used to develop novel drugs to prevent these diseases





Paolo Poggio



PICASSO

Unravelling proprotein convertase subtilisin/kexin type 9 (PCSK9) mechanisms in calcific aortic valve disease: from aortic valve sclerosis to stenosis

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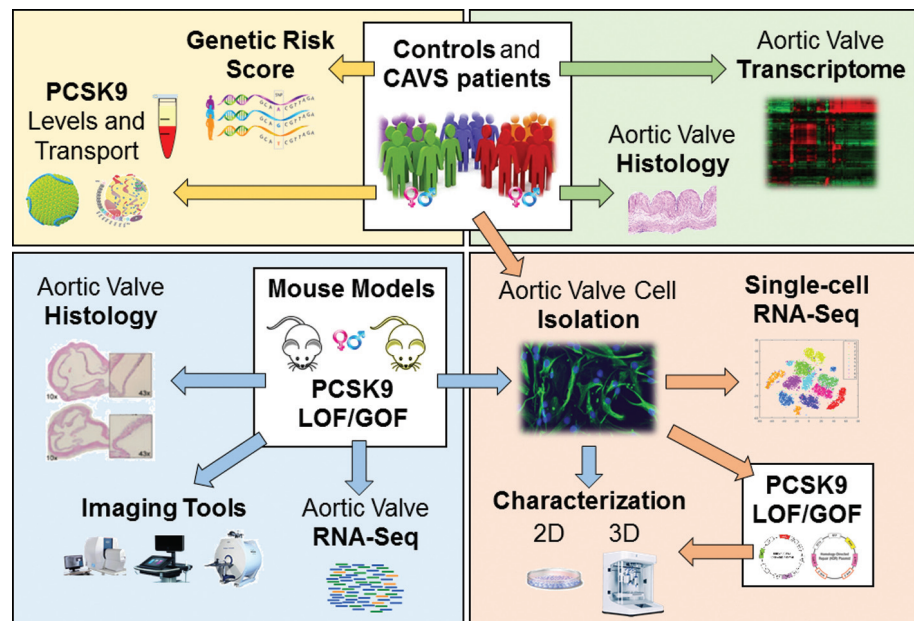
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Romain Capoulade, INSERM – Nantes University, France



Calcific aortic valve stenosis (CAVS) is a fatal pathology that affects 2-3% of the population. Yet, drug therapies are ineffective, leaving the urgency to fully characterize the etiology of aortic valve calcification to develop innovative therapies.

Our preliminary data suggest that PCSK9, an important protein for lipid metabolism, plays an active role in CAVS. Therefore, we will determine whether PCSK9 is a causal risk factor for CAVS using genetic epidemiology. Further, we will shed light on the molecular underpinnings through which PCSK9 causes CAVS in humans using state-of-the-art in vivo as well as in vitro models in combination with next-generation sequencing. As a complementary and potential preclinical model, we will determine the role of PCSK9 in the development of aortic valve calcification in mice.

The overarching aim of this research program is to provide the required biological evidence using a highly translational approach to support PCSK9 as a therapeutic target for the prevention and treatment of patients with CAVS.



Dissecting Mesenchymal-ENDothelial cross-talk, heterogeneity and function to mend vascular AGEing and atherosclerosis

Rafael Kramann, Uniklinik RWTH Aachen, Germany

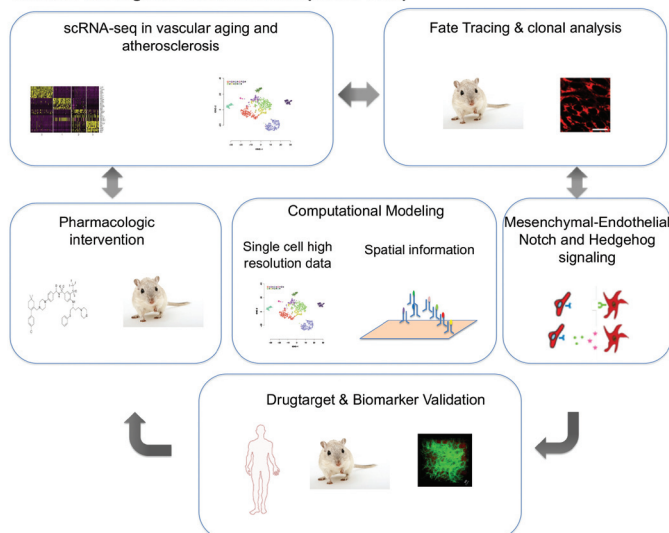
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Judith Sluimer, Maastricht University Medical Center, The Netherlands (Associated partner)

Aging increases cardiovascular events through cell senescence with accelerated atherosclerosis, fibrosis, endothelial dysfunction, oxidative stress (ROS), and inflammation. Resident mesenchymal cells (MCs), may not only drive fibrosis, but their cross-talk with smooth muscle, immune and endothelial cells (ECs) also affects angiogenesis, vascular tone, calcification and inflammation. Indeed, our consortium identified migrated MC driving atherosclerotic plaque calcification. Here, the molecular targets underlying the cellular ageing and cross-talk will be unveiled. We will: 1) analyse adventitial cell heterogeneity, fate and cross talk in arterial aging and atherosclerosis, 2) identify aging-induced drivers of vascular disease and 3) target aging-induced drivers in animal models to ameliorate aging-associated vascular pathology. The passion that drives this project is driven by a simple emerging hypothesis: It is possible to treat atherosclerosis and plaque rupture by synergizing endothelial-mesenchymal cross-talk to prevent excessive matrix production, angiogenesis, and inflammation.





Janine van Gils



MISs-CVD

Neuroimmune guidance cues, MicroRNAs & Inflammatory responses: Sex differences in CardioVascular Diseases

Coordinator:

Janine van Gils , Leiden University Medical Center, The Netherlands

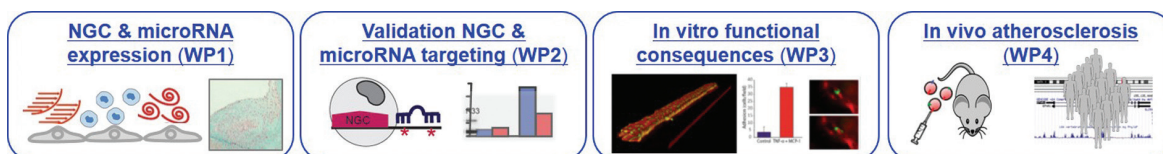
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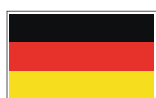
Hilal Kazan, Antalya Bilim University, Turkey



Cardiovascular disease remains number one cause of premature death in women. Despite advances in the diagnosis, prevention and treatment of cardiovascular disease, the risk of coronary artery disease in women, increases dramatically after menopause. In this MISs-CVD project we aim to better understand sex-specific biology in the vessel wall. We study specifically, sex-biased non-coding microRNAs that can regulate proteins that 'guide' white blood cells playing a role in the development of arteriosclerosis. This will provide crucial understanding of the gender differences in atherosclerosis and may deliver gender specific therapeutic avenues to combat atherogenesis in both men and women.



Bram Slütter



AtheroInside

Local immunomodulation of atherosclerosis by CD8⁺ t-cell based nanomedicines

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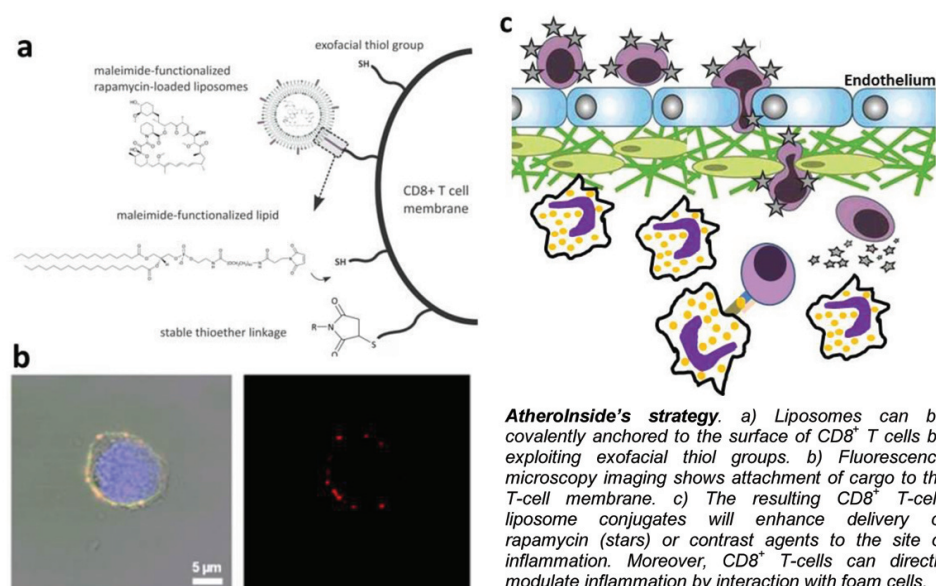
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Atherosclerosis, the progressive narrowing of blood vessels due to the build-up of plaque in the vessel wall, is the most important underlying cause of cardiovascular events, like heart attack or stroke. Recent clinical trials show a promising reduction of events through administration of anti-inflammatory drugs. However, the downside of treatment with anti-inflammatory drug is systemic immune suppression and an increased chance of lethal infections. In this project, we aim to gain a better understanding of inflammation inside the atherosclerotic lesion, which should allow us to design more specific anti-inflammatory therapies, without systemic immune suppression. We will investigate how immune cells infiltrate the atherosclerotic lesion and use these cells as vehicles to carry anti-inflammatory drugs into the lesion. Moreover, by retrofitting these cells with contrast agents, we expect them to enhance imaging of atherosclerotic lesion, with the goal of improving diagnostics. We anticipate that this project will increase our understanding of the inflammatory pathways inside the atherosclerotic lesion and potentially provide new strategies to visualize atherosclerotic lesions and reduce cardiovascular events.





Aoife Gowran



DENIM

Duchenne muscular dystrophy cardiomyopathy; the role of ENdocannabinoids and IMMune regulation

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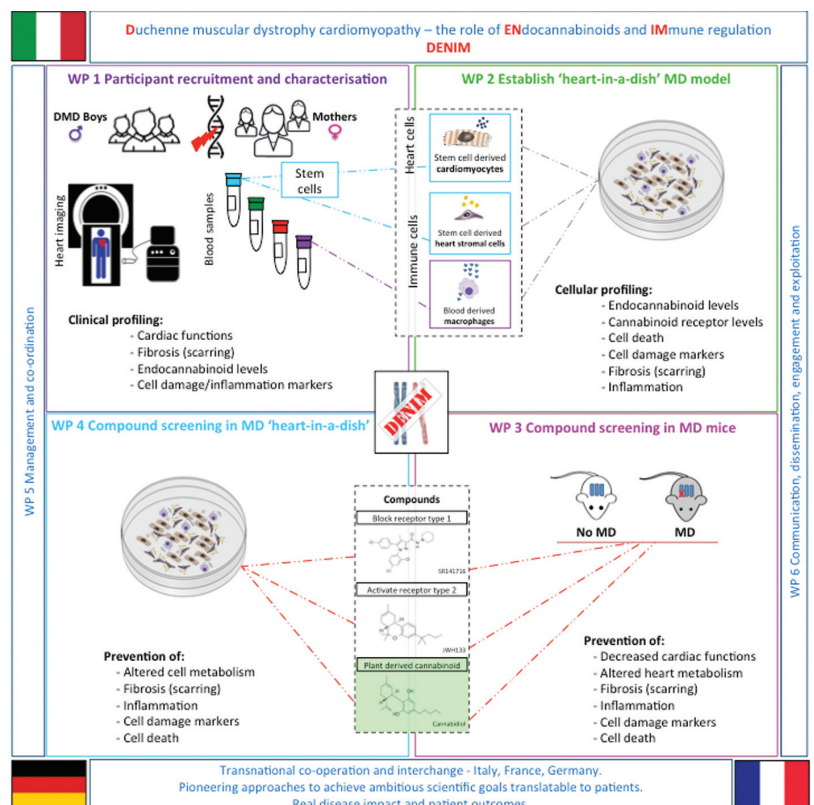
Lise Lefèvre, INSERM, Institute of Metabolic and Cardiovascular Diseases, France

Andrea Schrepper, University Hospital Jena, Germany

Giulio Pompilio, IRCCS Centro Cardiologico Monzino, Italy (Associated partner)

Muscular dystrophy (MD) is a genetic condition that causes muscles to degenerate and it affects young boys and some of their mothers. It is of great importance to find new therapies for MD, since existing therapy has limited effect and one of the leading causes of death is premature heart failure. Endocannabinoids are lipids in the human body that regulate many body processes by activating two types of cannabinoid receptor. We use heart cells made from MD patients' stem cells

to recreate MD heart disease in the lab. Using these patients' 'hearts-in-dishes' we showed that levels of endocannabinoids and cannabinoid receptors were changed. We also uncovered that modulating cannabinoid receptors protected MD heart cells and a non-psychoactive plant cannabinoid compound prevented the death of MD heart cells. Another aspect of our research shows that the immune system contributes to MD heart disease, thus we will incorporate immune cells to our model; forming a superior multi-cell MD heart disease model. We will test the protective effects of cannabinoid-based compounds in this 'heart-in-a-dish' MD model and in MD mice.





Sebastian Clauss



DETECT ARRHYTHMIAS

Investigating DETERminants of atrial Electrical Conduction underlying ARRHYTHMIAS

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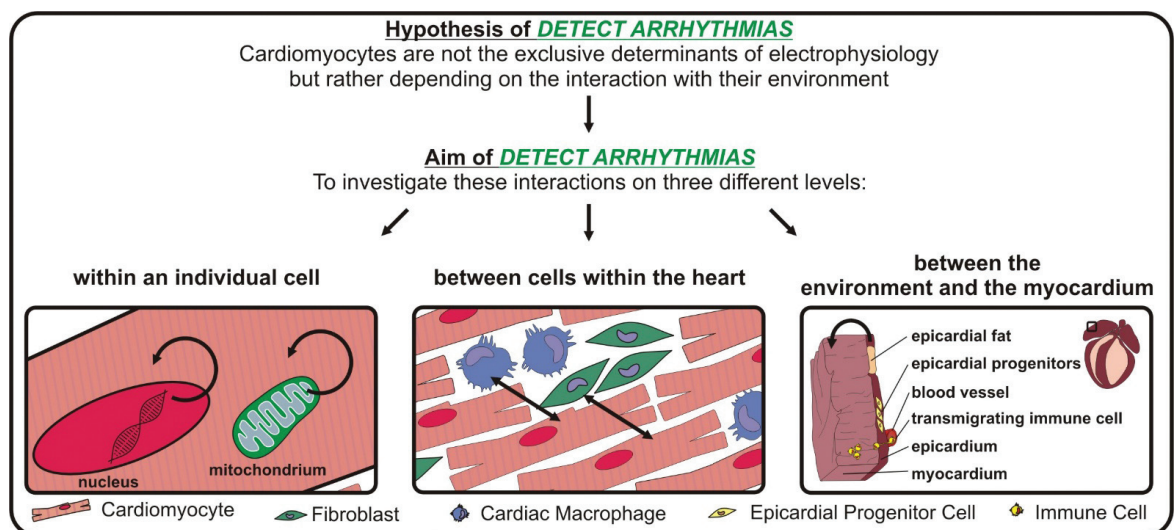
Davide Rovina, IRCCS Cardiologico Monzino, Italy

Fatih Kocabas, Yeditepe University, Turkey

Tõnu Esko, University of Tartu, Estonia

Arrhythmias are one of the major healthcare challenges since they are affecting millions of Europeans and are associated with significant morbidity and mortality. Current treatment options have to be improved by innovative therapies that are ideally targeting causal proarrhythmic mechanisms.

DETECT ARRHYTHMIAS is based on the hypothesis that cardiomyocytes are not the exclusive determinants of electrical conduction properties. The consortium will therefore investigate the cardiac “interactome” and its effects on physiologic impulse generation and propagation through the heart as well as on pathophysiologic mechanisms leading to arrhythmias. To this purpose we will study (epi)genetic, metabolic, electrophysiologic and immunologic factors on the level of individual myocardial cells, neighboring cells within the myocardium, and cells originating from outside of the myocardium.





Julia Binder



HyperDiP

Maternal hemodynamics in hypertensive disorders of pregnancy – a human and animal model under antihypertensive therapy

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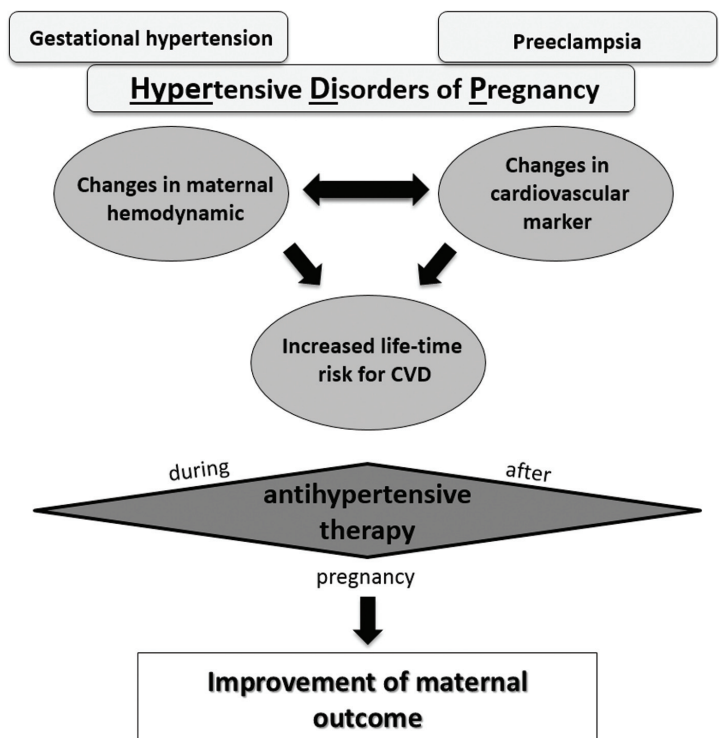
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Nadine Haase, Max-Delbrueck Center for Molecular Medicine in the Helmholtz Association (MDC), Germany

Hypertensive disorders of pregnancy (HDP) are still the leading cause of maternal and neonatal morbidity and mortality worldwide. Recently, a number of studies reported cardiovascular changes in pregnancies affected by HDP suspecting a cardiovascular origin of the disease. Even though there are new insights the concepts of therapy have not changed and evidence for an improvement of antihypertensive therapy (AT) in women with HDP is lacking. Therefore we aim to investigate maternal hemodynamics and cardiovascular parameters

in women with HDP compared to a healthy pregnant control group and in a preeclamptic rat model under AT. In this prospective observational case control study over a three-year period we challenge the idea of blood pressure being the suitable target for AT in women with HDP and aim to get new insights into the pathophysiology of preeclampsia by using invasive procedures and assessing the structural morphology of the heart in our rat model.





Moore-Morris Thomas



FIBER

Fibrosis Treatment by Enhancer Targeting

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Justus Stenzig, University Medical Center Hamburg-Eppendorf, Germany

Heart failure severely affects patients' quality of life and is a major cause of mortality of adult women and men. In a failing heart, cells named fibroblasts become activated and produce large amounts of scar tissue, a pathological process known as fibrosis. Recent studies have shed light on how to distinguish fibroblasts from other cell types and where the increased numbers of fibroblasts observed in heart failure come from. This project aims to identify interactions among genome regulatory sequences that drive fibroblast activation in heart disease. Such "epigenetic" changes are potentially reversible; hence, this may provide the scientific and medical communities with novel therapeutic targets against the progression of heart failure. To achieve this, fibroblasts from a mouse model of heart failure as well as patient tissue samples will be analysed. We will then test the therapeutic potential of disrupting candidate regulatory sequence interactions in fibroblasts in mouse and human engineered heart tissue (EHT) heart failure models.

